

## Complete Summary

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### GUIDELINE TITLE

Chemotherapy with radiotherapy for nasopharyngeal cancer.

### BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Thephamongkhol K, Browman G, Hodson I, Oliver T, Zuraw L. Chemotherapy with radiotherapy for nasopharyngeal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2004 Dec. 24 p. (Evidence-based series; no. 5-7). [31 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The Guideline will expand over time to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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## SCOPE

### DISEASE/CONDITION(S)

Newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV)

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

#### CLINICAL SPECIALTY

Oncology  
Otolaryngology  
Radiation Oncology

#### INTENDED USERS

Physicians

#### GUIDELINE OBJECTIVE(S)

To evaluate if the addition of chemotherapy to radiotherapy improves the survival of adult patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer and, if it does, to evaluate the best timing and regimen of chemotherapy

#### TARGET POPULATION

Adult patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV) who are being considered for radiotherapy as the definitive modality for curative intent and who can tolerate chemotherapy, in the judgement of the treating oncologist

#### INTERVENTIONS AND PRACTICES CONSIDERED

1. Radiation alone
2. Chemotherapy plus radiotherapy

#### MAJOR OUTCOMES CONSIDERED

- Tumour response
- Local control
- Overall survival
- Disease-free survival
- Adverse events
- Quality of life

### METHODOLOGY

#### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

#### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature was searched using MEDLINE (OVID; 1966 through October 2004), EMBASE (OVID; 1980 through October 2004), the Cochrane Library (OVID; Issue 3, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1997-2004), the American Society for Therapeutic Radiology and Oncology (1992-2004), the Asian Clinical Oncology Society (2001), the International Congress of Radiation Oncology (1997 and 2001), the European Society of Therapeutic Radiology and Oncology (1992, 1994, 1996, 1998, 2000, 2002), and the European Society for Medical Oncology (2000, 2002). Article bibliographies and personal files were also searched for evidence relevant to this report.

The literature search combined nasopharyngeal disease specific terms (nasopharyngeal neoplasms/ or nasopharynx: .mp. or nasopharyngeal.tw.) with treatment specific terms (drug therapy/ or chemotherapy/ or chemotherapy.tw. or radiochemotherapy.mp. or chemoradiotherapy.mp.) and search specific terms for the following: practice guidelines, systematic reviews, meta-analyses, and randomized controlled trials.

### Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published reports or published abstracts of randomized controlled trials that reported the following:

- Data on the treatment population of interest (i.e., newly diagnosed patients with locally advanced squamous cell or undifferentiated nasopharyngeal cancer)
- Data on patients receiving any combination of chemotherapy plus radiation in the neoadjuvant, concurrent, or adjuvant setting (intervention) versus radiotherapy alone (control)
- Results for the primary outcomes of interest: disease-free survival and/or overall survival, or for the secondary outcomes of interest: local control, response, toxicity, and/or quality of life

Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also eligible for inclusion in the systematic review.

### Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they:

- Were trials that did not report separate results for patients with nasopharyngeal cancer
- Were trials reported in a language other than English where data could not be extracted

### NUMBER OF SOURCE DOCUMENTS

Nineteen randomized controlled trials and 3 meta-analyses were eligible for inclusion and review.

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

## METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials  
Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Combining results across trials provides added power for detecting the efficacy of the treatment and improves the reliability or confidence of the point estimate. Where appropriate, data on outcomes of interest are pooled across trials using a clinically relevant event or time-point. In this report, the common time-point of two years was selected, as most of the trials reported sufficient follow-up (greater than 50%) at two years, and two-years is a clinically reliable time-point to detect differences in recurrence or survival outcomes in this patient population. Where two-year survival data were not reported, data were estimated from published survival curves, or in the case of missing data, authors were contacted for further information. Individual patient data were not available for these analyses.

Data are pooled using Review Manager 4.0.3 (Metaview© Update Software), available through the Cochrane Collaboration ([www.cochrane.org](http://www.cochrane.org)). Results are expressed as the Odds Ratio (OR) with 95% confidence intervals (CI), where an OR less than 1.0 favours the experimental treatment and an OR greater than 1.0 favours control. The random effects model is generally preferred over the fixed effects model as the more conservative estimate of effect. The number of patients needed to treat for one additional patient to benefit (NNT) is calculated using the inverse of the risk difference. In pooling the data, multiple treatment arms are categorized as separate trials comparing each treatment arm with the same control arm. Where appropriate, sensitivity analyses are conducted to determine whether particular study characteristics influence the estimate of treatment effect.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The draft recommendations, which were sent to Ontario Practitioners, were largely driven by the only randomized trial (at the time) to detect an improvement in overall survival. However, there were significant concerns with the existing body of evidence, and in the absence of further data, current practice and the best available evidence was used as the basis of the draft recommendations. After practitioner feedback was completed, the recommendations were strengthened significantly to reflect the introduction of new trial evidence that was positive. That trial confirmed that cisplatin-based chemotherapy was more effective than radiotherapy alone. As a result of the external review process and the introduction of new data over time, the final recommendations have changed substantially from the original iteration.

With evidence from the systematic review of the data, consensus among Disease Site Group (DSG) members, feedback obtained from practitioners within Ontario, approval from the Practice Guideline Coordinating Committee, and the introduction of new data, the Head and Neck Cancer Disease Site Group finalized recommendations for adult patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV). For patients who are considered for radiotherapy as the definitive modality for curative intent and who can tolerate chemotherapy, in the judgement of the treating oncologist, radiochemotherapy was recommended over radiotherapy alone. Specifically cisplatin-based concurrent radiochemotherapy, with or without adjuvant chemotherapy was recommended as the preferred regimen and timing of chemotherapy.

#### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

#### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

#### METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

#### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

As part of the Program in Evidence-based Care (PEBC's) Clinical Practice Guideline Development Cycle, all reports are sent to Ontario practitioners for external review. Descriptions of the process have been previously described. External reviewers receive a practitioner feedback package comprised of a copy of the draft systematic review, the draft clinical practice guideline with recommendations and a standardized survey that addresses the rigour and quality of the methods, results and interpretations of the evidence used to inform the recommendations, and whether the draft recommendations should serve as a practice guideline.

In this series practitioner feedback was obtained through a mailed survey of 52 practitioners in Ontario (12 medical oncologists, 24 radiation oncologists, and 16 surgeons). Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again).

The practice guideline report was circulated to 14 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Seven of the 14 members returned ballots. Six PGCC members approved the practice guideline report as written. One member approved the report, with the following modifications required:

1. Further clarification on the impact of patient histology and ethnicity on the applicability of the results to patients in Ontario should be provided.
2. Given the substantive changes from the draft to the final recommendations, the PGCC member suggested that the process of evidence acquisition should be explained in more detail.
3. Data on absolute improvement with chemotherapy and radiotherapy compared with radiotherapy alone should be added.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- It is recommended that cisplatin-based concurrent radiochemotherapy be routinely offered to patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV).
- Of the four trials with cisplatin-based concurrent chemotherapy that showed a significant overall survival difference, two included adjuvant chemotherapy, while two did not. It is recommended that either treatment approach may be offered to this patient population.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- Pooled results across trials detected overall survival benefits with radiochemotherapy when compared with radiotherapy alone (See Table 1 in the original guideline document for further details).

- By timing of chemotherapy, pooled results detected a significant overall survival advantage with cisplatin-based concurrent chemoradiotherapy with or without adjuvant chemotherapy. This is supported by four randomized trials that detected statistically significant overall survival benefits with cisplatin-based chemoradiotherapy when compared to radiotherapy alone (See Table 1 in the original guideline document for further details).

## POTENTIAL HARMS

- Table 3 in the original guideline document outlines the commonly reported adverse events related to treatment with chemotherapy.
- Where reported, severe grade 3/4 toxicity associated with chemotherapy ranged from 0 to 18% for anemia, 1 to 6% for febrile neutropenia, 0 to 8% for thrombocytopenia, 2 to 38% for leucopenia, 4 to 49% for nausea/vomiting, and 0 to 8% for toxic deaths. In addition, 0 to 84% of patients experienced some grade of alopecia. One trial reported a significant difference in hearing loss in patients treated with radiochemotherapy compared with radiotherapy alone (23% versus 7%;  $p=0.02$ ). One trial reported 22 patients with grade 3 neutropenia, two patients with neutropenic fever, and significant increase in loss of body weight with the addition of chemotherapy to radiotherapy. With the exception of two trials reporting significant increases in mucositis with radiochemotherapy, acute radiation toxicity did not differ significantly between any of the treatment groups in any of the trials.
- Nine of the nineteen randomized trials reported rates of toxic death with radiochemotherapy versus radiotherapy alone. Toxic death rates ranged from 0% to 8% for patients in the radiochemotherapy arms versus 0% to 2.5% for patients in the radiotherapy arms. The differences in toxic death were significant in only one trial which utilized an aggressive chemotherapy regimen.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- If concurrent chemotherapy is chosen, the recommended regimen, with the greater magnitude of effect and an acceptable toxicity profile, consists of cisplatin 20 mg/m<sup>2</sup>/day and 5-fluorouracil 400 mg/m<sup>2</sup> as a 96-hour continuous infusion during weeks 1 and 5 of conventionally fractionated radiotherapy.
- If concurrent and adjuvant chemotherapy is chosen, the recommended regimen consists of three doses of cisplatin 100 mg/m<sup>2</sup> administered concurrently on days 1, 22, and 43 of conventionally fractionated radiotherapy. In the adjuvant setting, it is recommended that 80 mg/m<sup>2</sup> of cisplatin be combined on day 1 with 1,000 mg/m<sup>2</sup> fluorouracil as a four-day continuous infusion for three monthly cycles starting four weeks after completion of radiation.
- Patients with World Health Organization types 1, 2, and 3 nasopharyngeal carcinoma were included in both of the recommended chemotherapy regimens; however, stratified analyses by histology were not performed in the randomized trials.

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Thephamongkhol K, Browman G, Hodson I, Oliver T, Zuraw L. Chemotherapy with radiotherapy for nasopharyngeal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2004 Dec. 24 p. (Evidence-based series; no. 5-7). [31 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2003 Jul 22 (revised 2004 Dec)

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT



The Program in Evidence-based Care (PEBC), is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

#### SOURCE(S) OF FUNDING

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care

#### GUIDELINE COMMITTEE

Provincial Head and Neck Cancer Disease Site Group

#### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

#### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Disease Site Group disclosed potential conflict of interest information.

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#### GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

#### AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Chemotherapy with radiotherapy for nasopharyngeal cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

#### PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on June 29, 2004. The information was verified by the guideline developer on July 19, 2004. This NGC summary was updated by ECRI on August 12, 2005. The updated information was verified by the guideline developer on September 13, 2005.

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